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A Prospective Randomized Trial of Pancreaticogastrostomy *Versus* Pancreaticojejunostomy After Pancreaticoduodenectomy

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Objective

The authors hypothesized that pancreaticogastrostomy is safer than pancreaticojejunostomy afte pancreaticoduodenectomy and less likely to be associated with a postoperative pancreatic fistula

Summary Background Data

Pancreatic fistula is a leading cause of morbidity and mortality after pancreaticoduodenectomy, occurring in 10% to 20% of patients. Nonrandomized reports have suggested that pancreaticogastrostomy is less likely than pancreaticojejunostomy to be associated with postoperative complications.

Methods

Between May 1993 and January 1995, the findings for 145 patients were analyzed in this prospective trial at The Johns Hopkins Hospital. After giving their appropriate preoperative informed consent, patients were randomly assigned to pancreaticogastrostomy or pancreaticojejunostomy after completion of the pancreaticoduodenal resection. All pancreatic anastomoses were performed in two layers without pancreatic duct stents and with closed suction drainage. Pancreatic fistula was defined as drainage of greater than 50 mL of amylase-rich fluid on or after postoperative day 10.

Results

The pancreaticogastrostomy (n = 73) and pancreaticojejunostomy (n = 72) groups were comparable with regard to multiple parameters, including demographics, medical history, preoperative laboratory values, and intraoperative factors, such as operative time, blood transfusions, pancreatic texture, length of pancreatic remnant mobilized, and pancreatic duct diameter. The overall incidence of pancreatic fistula after pancreaticoduodenectomy was 11.7% (17/145). The incidence of pancreatic fistula was similar for the pancreaticogastrostomy (12.3%) and pancreaticojejunostomy (11.1%) groups. Pancreatic fistula was associated with a significant prolongation of postoperative hospital stay (36 ± 5 *vs.* 15 ± 1 days) ($p < 0.001$). Factors significantly increasing the risk of pancreatic fistula by univariate logistic regression analysis included ampullary or duodenal disease, soft pancreatic texture, longer operative time, greater intraoperative red blood cell transfusions, and lower surgical volume ($p < 0.05$). A multivariate logistic regression analysis revealed the factors most highly associated with pancreatic fistula to be lower surgical volume and ampullary or duodenal disease in the resected specimen.

Conclusions

Pancreatic fistula is a common complication after pancreaticoduodenectomy, with an incidence most strongly associated with surgical volume and underlying disease. These data do not support the hypothesis that pancreaticogastrostomy is safer than pancreaticojejunostomy or is associated with a lower incidence of pancreatic fistula.

Pancreaticoduodenectomy has become increasingly accepted as a safe and appropriate operation for selected patients with malignant and benign diseases of the pancreas and periampullary region. The operative mortality rate after pancreaticoduodenectomy is 4% or less at major surgical centers.[1-5] Postoperative sepsis, hemorrhage, and cardiovascular events are responsible for the majority of deaths after pancreaticoduodenectomy.

Although the mortality rate after pancreaticoduodenectomy has decreased in recent years, the incidence of postoperative morbidity occasionally approaches 50%.[1-8] In most series, the three leading causes of morbidity after pancreaticoduodenectomy are delayed gastric emptying, wound infection, and pancreatic fistula resulting from a pancreatic anastomotic leak.[1,2,8-11] Failure of a pancreatic–enteric anastomosis to heal after pancreaticoduodenectomy can be a source of considerable morbidity and can contribute to mortality. The incidence of pancreatic anastomotic leak ranges from 5% to 25% in most series. Because pancreatic fistula has been such a common problem after pancreaticoduodenectomy, various techniques of managing the pancreatic remnant (body and tail of the pancreas) have been studied.[12] Simple suture ligation of the pancreatic duct without enteric anastomosis was popular in past decades,[13] but has been largely abandoned due to an external fistula rate of more than 50%.[14] Pancreatic ductal occlusion with such substances as neoprene or prolamine has been proposed as a means of reducing fistula rates, with some reported success.[15,16] Various modifications of a pancreaticojejunal anastomosis have been tested, including site of jejunum used (end *vs.* side), type of anastomosis (invagination *vs.* duct-to-mucosa), use of an isolated Roux-en-Y limb, and use of fibrin glue and pancreatic duct stenting.[17-22] No universal agreement has been reached regarding one particular variation of pancreaticojejunostomy being safer and less prone to fistula formation.

A recently repopularized option for enteric drainage of the pancreatic remnant is pancreaticogastrostomy, a technique first reported on experiments in dogs in 1934[23] and used clinically for 50 years.[24,25] Reported results of pancreaticogastrostomy have been favorable, with very low rates of pancreatic fistula and mortality.[26-29]

To our knowledge, there has been no prospective randomized comparison between pancreaticogastrostomy and pancreaticojejunostomy after pancreaticoduodenectomy in humans. This prospective randomized single-institution trial was designed to test the hypothesis that pancreaticogastrostomy is safer than pancreaticojejunostomy and less likely to be associated with a postoperative pancreatic fistula.

METHODS

This study was approved by the Joint Committee on Clinical Investigation of the Johns Hopkins University School of Medicine. Patients were recruited into the study preoperatively, and appropriate informed consent was obtained. Between May 1993 and January 1995, 176 patients underwent pancreaticoduodenectomy at the Johns Hopkins Hospital. Of these, 146 patients (83%) were enrolled in this study. The reasons for nonenrollment of the remaining 30 patients were total pancreatectomy (n = 10), resection by nonparticipating surgeons (n = 16), and patient never recruited (n = 4).

Randomization and Exclusions

Enrolled patients (n = 146) were randomized intraoperatively after pancreaticoduodenal resection to either the pancreaticogastrostomy (PG) or pancreaticojejunostomy (PJ) group by means of a randomly generated number pattern. After enrollment and randomization, 1 patient was excluded from the analysis, leaving 145 patients in the study population. The patient who was excluded from analysis developed multisystem organ dysfunction after surgery. A postoperative computed tomography scan demonstrated large infarcts of the liver, spleen, and kidneys, presumed to be related to catheter-

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induced thromboemboli at the time of the preoperative arteriogram, which was performed for staging purposes. The patient required re-exploration for bleeding on the 12th postoperative day and died on the 22nd postoperative day.

Surgical Technique

Pancreaticoduodenal resection was performed as a partial pancreatectomy, with either classic resection (to include distal gastrectomy) or the pylorus-preserving modification.[30,31] Octreotide was not used prophylactically in any patient, but was used postoperatively at the primary surgeon's discretion. Vagotomy, tube gastrostomy, or feeding jejunostomy was not performed in any patient. All hepaticojejunal anastomoses were stented (decompressed) through an operatively placed T tube or a preoperatively placed percutaneous transhepatic catheter. At the completion of the pancreaticoduodenal resection, the length of mobilization of the pancreatic remnant and the diameter of the pancreatic duct (at the transected edge of the pancreatic neck) were measured. All pancreatic anastomoses were hand sewn and performed in two layers: 3-0 silk for the outer layer and 3-0 polyglactin (Vicryl; Ethicon, Johnson and Johnson, Somerville, NJ) for the inner layer. Pancreatic duct stents and fibrin glue were not used.

Pancreaticojejunostomy was performed in either end-to-end or end-to-side fashion at the surgeon's discretion, as previously described.[30] End-to-end PJ was favored and was most commonly performed (n = 48). End-to-side PJ was used (n = 24) when there was a size discrepancy between a jejunum with a relatively small diameter and a pancreatic segment with a relatively large transected end. For either end-to-end or end-to-side PJ, the retained jejunum was brought through a rent in the right transverse mesocolon, with the PJ being performed to the proximal-most jejunum, followed by a standard end-to-side hepaticojejunostomy and an end-to-side duodenojejunostomy or gastrojejunostomy. We accomplished pancreaticogastrostomy by anastomosing the pancreatic remnant to the posterior gastric wall midway between the lesser and greater curvature, at least 7 cm proximal to the pylorus or distal gastric staple line. The size of the posterior gastrotomy averaged 2.5 to 3 cm (Fig. 1).

At the conclusion of the pancreaticoduodenal reconstruction, one or two ¼-inch round silicone closed-suction drains (ReliaVac; Davol, Cranston, RI) were introduced through separate left-sided abdominal stab incisions and placed in the vicinity of the pancreatic anastomosis. Additionally, one or two ¼-inch round silicone closed-suction drains were introduced through separate right-sided abdominal stab incisions and placed in the vicinity of the hepaticojejunostomy.

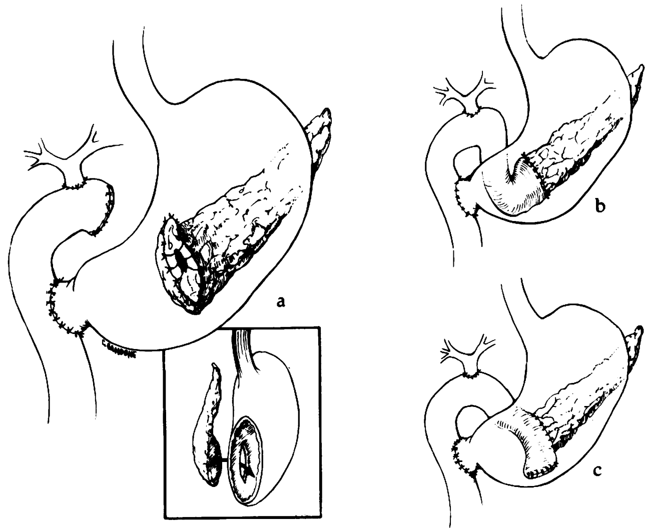

Figure 1. Schematic illustration of (A) pancreaticogastrostomy, (B) end-to-end pancreaticojejunostomy and (C) end-to-side pancreaticojejunostomy. (Inset) Detailed pancreaticogastrostomy, indicating the location of the posterior gastrotomy.

Postoperative Management

Operatively placed drains in the vicinity of the pancreatic anastomosis were left undisturbed, with their outputs recorded daily for at least 5 postoperative days. Aliquots of the drainage were sent for amylase determination between postoperative days 3 and 7. A cholangiography, obtained through the T tube or percutaneous transhepatic catheter, and, in most cases, a water-soluble upper gastrointestinal series[32,33] were performed on postoperative days 4 to 7 and were used to assess for leakage or obstruction at any of the three reconstructive anastomoses. In the absence of a pancreatic fistula (radiographically documented leak or >50 mL drainage of amylase-rich fluid on or after postoperative day 10), the drains were removed. In the presence of a pancreatic fistula, management was left to the discretion of the primary surgeon.

All patients received histamine H_2-receptor antagonists (e.g., ranitidine, famotidine) during their postoperative hospitalization as prophylaxis for stress and marginal ulceration. The majority of patients received intravenous erythromycin lactobionate (200 mg intravenously every 6 hours from postoperative day 3 to 10) as prophylaxis for delayed gastric emptying.[10]

Data Collection

The preoperative, intraoperative, and postoperative care of each patient was directed by the attending surgeon, including the use and duration of prophylactic antibiotics, type of nutritional support, and time of removal of the nasogastric tube and operatively placed drains. Data were collected prospectively on all patients and included historic information, details of the operative procedure, a surgeon questionnaire (detailing such factors as pancreatic texture [soft, intermediate, hard], duct diameter, length of pancreatic remnant, and drain contact with the anastomosis), disease of the resected specimen, results of postoperative gastrointestinal contrast studies, and clinical information regarding the postoperative course (both in-hospital and after discharge).

Study End Points

The primary study end point was pancreatic fistula, defined as (1) drainage of greater than 50 mL of amylase-rich fluid (greater than threefold elevation above upper limit of normal in serum) through the operatively placed drains on or after postoperative day 10 or (2) pancreatic anastomotic disruption demonstrated radiographically.

Secondary study end points included assessment of postoperative complications (defined as those occurring during the hospitalization and including abdominal and extra-abdominal complications), length of postoperative hospital stay, and correlations between pancreatic fistula and multiple preoperative, intraoperative, and postoperative parameters.

Statistical Analyses

Study Design. The number of patients predicted to be necessary for statistical validity was based on the premise of improving the rate of pancreatic fistula from 20% to 5%, with alpha set at 0.05 and beta set at 0.2, yielding a power of 80%. We calculated that 72 patients would be required in each arm of the study, for a total projected study population of 144 patients.

Comparability of the PG and PJ groups was verified with Student's t tests and chi square statistics. When t tests were used, variables with skewed distributions were transformed by means of a natural logarithm. Factors associated with pancreatic fistula were selected based on cross-tabulations and logistic regression modeling. Cross-tabulations were analyzed with chi square or Fisher's exact tests, where appropriate. A stepwise logistic regression model[34] was used to determine the effects of multiple factors on pancreatic fistula. Significance was accepted at the 5% level. All confidence intervals were reported at the 95% level. Data are presented as mean ± standard error of the mean. All statistical computations were performed with the SAS (Statistical Analysis System) or EGRET (Statistics and Epidemiologic Research Corp.) personal computer packages.[35,36]

Table 1. PATIENT CHARACTERISTICS AND PREOPERATIVE PARAMETERS

	PG (n = 73)	PJ (n = 72)	p Value
Age (yr)	61.5 ± 1.7	62.4 ± 1.4	NS
Gender			
Male	33 (45)	38 (53)	NS
Female	40 (55)	34 (47)	NS
Race			
White	66 (90)	66 (92)	NS
Black	5 (7)	5 (7)	NS
Other	2 (3)	1 (1)	NS
Preoperative history			
Jaundice	44 (60)	45 (63)	NS
Weight loss	34 (47)	36 (50)	NS
Abdominal pain	33 (45)	34 (47)	NS
Smoking	31 (42)	28 (39)	NS
Prior abdominal surgery	27 (37)	32 (44)	NS
Hypertension	22 (30)	30 (42)	NS
Alcohol use	22 (30)	18 (25)	NS
Peptic ulcer disease	10 (14)	11 (15)	NS
Diabetes	9 (12)	11 (15)	NS
Preoperative laboratory values			
Hematocrit (%)	37.1 ± 0.6	36.8 ± 0.6	NS
White blood cell count (10^3 cells/mm^3)	9.3 ± 0.5	9.1 ± 0.4	NS
Creatinine (mg/dL)	1.1 ± 0.1	1.1 ± 0.1	NS
Total bilirubin (mg/dL)	7.4 ± 2.5	5.8 ± 0.9	NS
Albumin (g/dL)	3.7 ± 0.1	3.7 ± 0.1	NS
Preoperative hospital stay (days)	2.1 ± 1.5	2.9 ± 1.5	NS

PG = pancreaticogastrostomy; PJ = pancreaticojejunostomy; NS = not significant.
Values in parentheses are percentages.

RESULTS

Patient Population

The study population consisted of 145 patients with a mean age of 61.9 ± 1.1 years. Seventy-one patients (49%) were male, and 74 patients were female (51%). One hundred thirty-two patients (91%) were white. Seventy-three patients were randomized to the PG group and 72 to the PJ group. No differences were observed between the PG and PJ groups on comparison of multiple patient characteristics and preoperative parameters (Table 1).

The pylorus-preserving modification of pancreaticoduodenectomy was performed in 119 patients (82%), whereas classic pancreaticoduodenectomy was performed in 26 patients (18%). No significant differences between the PG and PJ groups were observed on comparison of multiple intraoperative parameters (Table 2). The pathologic findings in the resected specimens revealed malignant disease in 122 patients (84%) and benign disease in 23 patients (16%). Eighty patients (55%) had malignant tumors of the pancreas.

Table 2. INTRAOPERATIVE PARAMETERS

	PG (n = 73)	PJ (n = 72)	p Value
Type of resection			
Pylorus-preserving	60 (82)	59 (82)	NS
Classic	13 (18)	13 (18)	NS
Operative time and blood			
Operative time (hr)	7.4 ± 0.2	7.2 ± 0.2	NS
Blood loss (mL)	964 ± 118	849 ± 126	NS
Blood replacement (units of erythrocytes)	0.9 ± 0.3	0.9 ± 0.3	NS
Pancreas factors			
Texture at transected neck			
Hard	21 (29)	28 (39)	NS
Intermediate	36 (49)	27 (37)	NS
Soft	16 (22)	17 (24)	NS
Mean length of remnant mobilized (cm)	3.1 ± 0.1	3.0 ± 0.1	NS
Mean diameter of pancreatic duct at transected neck (mm)	3.4 ± 0.2	2.9 ± 0.2	NS
Pancreatic duct in inner layer of anastomosis (%)	82	76	NS
Drains in contact with anastomosis (%)	82	74	NS
Pathology			
Pancreas			
Malignant	40 (55)	40 (56)	NS
Benign	11 (15)	7 (10)	NS
Bile duct			
Malignant	6 (8)	7 (10)	NS
Benign	0 (0)	0 (0)	NS
Ampulla			
Malignant	7 (10)	11 (15)	NS
Benign	2 (3)	0 (0)	NS
Duodenum			
Malignant	4 (5)	5 (7)	NS
Benign	3 (4)	0 (0)	NS
Other	0 (0)	2 (3)	NS

PG = pancreaticogastrostomy; PJ = pancreaticojejunostomy; NS = not significant.
Values in parentheses are percentages.

Table 3 describes the postoperative complications observed. Delayed gastric emptying was observed in 32 patients (22%), wound infection in 25 (17%), and pancreatic fistula in 17 (11.7%). The next most common complications were cholangitis in 10 patients (7%), pneumonia in 7 patients (5%), and intra-abdominal abscess in 6 patients (4%). No significant differences in the incidence of these individual complications were noted in a comparison of the PG and PJ groups. The total number of patients with any of these complications was similar, with 36 in the PG group (49%) and 31 in the PJ group (43%; p = NS). Additionally, no significant differences among the two groups were observed for total pancreatic drain output or length of hospital stay.

Pancreatic Fistula

The overall incidence of pancreatic fistula was 11.7% (17/145), which was similar for the PG (12.3%) and PJ (11.1%) groups. Table 4 lists the results of univariate logistic regression models constructed to assess the risk of pancreatic fistula based on patient demographics, preoperative parameters, type of anastomosis, intraoperative parameters, and surgical volume. Patient age, sex, and race did not significantly influence the rates of pancreatic fistula. Similarly, no preoperative parameters were significantly associated with pancreatic fistula. The type of anastomosis (PG *vs.* PJ) did not significantly influence the rate of pancreatic fistula formation. Intraoperative parameters that significantly increased the risk of pancreatic fistula were increasing operative time and blood replacement, soft pancreatic texture, and ampullary or duodenal disease. Finally, there were increasing odds ratios for pancreatic fistula, which was generally related to a decreasing patient volume per surgeon.

Table 3. POSTOPERATIVE FACTORS AND COMPLICATIONS

	PG (n = 73)	PJ (n = 72)	p Value
Delayed gastric emptying*	16 (22)	16 (22)	NS
Wound infection	14 (19)	11 (15)	NS
Pancreatic fistula†	9 (12)	8 (11)	NS
Cholangitis	4 (5)	6 (8)	NS
Pneumonia	5 (7)	2 (3)	NS
Intra-abdominal abscess	4 (5)	2 (3)	NS
Cardiac arrhythmia	3 (4)	2 (3)	NS
Bile leak	1 (1)	3 (4)	NS
Urinary tract infection	2 (3)	1 (1)	NS
Postoperative pancreatitis	1 (1)	1 (1)	NS
Peptic ulcer	2 (3)	0 (0)	NS
Duodenojejunostomy leak	0 (0)	2 (3)	NS
No. of patients with above complications	36 (49)	31 (43)	NS
No. of patients commencing total parenteral nutrition postoperatively	21 (29)	31 (43)	NS
Total output from pancreatic drains (mL)	1224 ± 166	1200 ± 177	NS
Postoperative hospital stay (days)	17.1 ± 1.6	17.7 ± 1.5	NS

NS = not significant.
Values in parentheses are percentages.
* Defined as follows: (1) nasogastric tube in place ≥ 10 days plus one of the following: (a) emesis after nasogastric tube removed, (b) reinsertion of nasogastric tube, or (c) failure to progress with diet; or (2) nasogastric tube in place < 10 days plus two of (a) to (c) above.
† Defined as follows: (1) drainage of > 50 mL of amylase-rich fluid (greater than threefold elevation above upper limit of normal in serum) via the operatively placed drains on or after postoperative day 10 or (2) pancreatic anastomotic disruption demonstrated radiographically.

Table 4. P VALUES, ODDS RATIOS, AND SELECTED 95% CONFIDENCE INTERVALS FOR PANCREATIC FISTULA FROM UNIVARIATE LOGISTIC REGRESSION MODELS

Parameter	p Value	Odds Ratio	CI
Demographics			
Age	0.10	1.04	
Gender	0.73	1.20	
Race	0.64	0.60	
Preoperative factors			
Diabetes	0.80	0.81	
Smoking	0.32	0.57	
Alcohol	0.14	0.32	
Jaundice	0.45	0.68	
Abdominal pain	0.55	1.36	
Hematocrit	0.94	1.00	
White blood count	0.12	1.01	
Total bilirubin	0.66	0.99	
Albumin	0.51	1.33	
Type of anastomosis			
PJ	—	1.00	
PG	0.82	1.13	
Intraoperative parameters			
Operative time	0.03	1.42	1.0–2.0
Blood loss	0.21	1.54	0.8–3.0
Blood replacement	0.008	1.30	1.1–1.6
Pancreatic texture			
Hard	—	1.00	—
Intermediate	0.51	1.61	0.4–6.8
Soft	0.03	4.91	1.2–20.2
Pancreatic remnant mobilized ≥ 3 cm	0.73	1.21	
Pancreatic duct diameter ≥ 3 mm	0.89	0.93	
Pancreatic duct included in inner layer	0.83	0.88	
Drains in contact with anastomosis	0.45	0.65	
Pathology			
Pancreas	—	1.00	—
Bile duct	0.83	1.28	0.1–11.5
Ampulla	0.01	5.11	1.4–18.9
Duodenum	<0.001	10.95	2.7–45.0
Patient volume per surgeon			
76	—	1.00	—
29	0.09	3.89	0.8–18.6
17	0.004	10.14	2.1–48.1
14	0.03	6.64	1.2–37.1
9	0.05	6.95	1.0–48.9

PJ = pancreaticojejunostomy; PG = pancreaticogastrostomy; CI = confidence interval.

In a stepwise multivariate logistic regression model (Table 5), the strongest predictors of pancreatic fistula were surgical volume and ampullary or duodenal disease. Such parameters as operative time and pancreatic texture, which were significant predictors of pancreatic fistula by univariate analysis, failed to maintain statistical significance in the multivariate model. Adjustment of the multivariate model for the strongest predictive factors of surgical volume and ampullary or duodenal disease revealed that the risk of pancreatic fistula in the PG group was 1.76 times the risk in the PJ group (p = 0.36; NS), with a wide confidence interval (0.5–5.9).

Table 5. MULTIVARIATE LOGISTIC REGRESSION MODEL FOR PANCREATIC FISTULA

Parameter	p Value	Odds Ratio	CI
Patient volume per surgeon			
76	—	1.00	—
29	0.120	3.83	0.7–20.8
17	0.005	12.96	2.1–78.3
14	0.069	6.00	0.9–41.3
9	0.029	11.62	1.3–105
Pathology			
Pancreas	—	1.00	—
Bile duct	0.329	3.31	0.3–36.6
Ampulla	0.024	5.43	1.3–23.7
Duodenum	0.001	12.63	2.6–60.3
Type of anastomosis			
PJ	—	1.00	—
PG	0.36	1.76	0.5–5.9

PJ = pancreaticojejunostomy; PG = pancreaticogastrostomy; CI = confidence interval.

Table 6 shows a comparison of multiple postoperative parameters for the 17 patients with pancreatic fistula to the 128 patients without pancreatic fistula. Many parameters are significantly different in a comparison of these

Table 6. COMPARISON OF PANCREATIC FISTULA TO NO PANCREATIC FISTULA GROUPS

	Pancreatic Fistula (n = 17)	No Fistula (n = 128)	p Value
Postoperative factors/ complications (%)			
Delayed gastric emptying	47	19	0.01
Wound infection	41	14	0.01
Cholangitis	24	5	0.02
Pneumonia	18	3	0.04
Intra-abdominal abscess	29	1	<0.001
Octreotide use postoperatively	100	14	<0.001
Commence TPN postoperatively	94	28	<0.001
Total output from pancreatic drains (mL)	3615 ± 522	893 ± 86	<0.001
Postoperative hospital stay (days)	36.4 ± 5.0	14.9 ± 0.8	<0.001

PG = pancreaticogastrostomy; PJ = pancreaticojejunostomy; TPN = total parenteral nutrition.

two groups, including delayed gastric emptying, wound infection, cholangitis, pneumonia, and intra-abdominal abscess formation, implying a relationship between pancreatic fistula and other complications. The higher frequencies of postoperative octreotide use and commencement of total parenteral nutrition reflect the use of these two therapies after recognition of a pancreatic fistula. The total output from the pancreatic drains was significantly larger in the group with pancreatic fistula, with there being no significant difference between the patients with pancreatic fistula in the PG (4137 ± 611 mL) and PJ groups (3027 ± 865 mL). The postoperative length of hospital stay for the patients with pancreatic fistula was 36.4 ± 5.0 days, which was significantly longer ($p < 0.001$) than the length of stay of 14.9 ± 0.8 days for patients without a pancreatic fistula.

DISCUSSION

Pancreatic fistula remains a major cause of morbidity after pancreaticoduodenectomy and can contribute to mortality. The most common techniques for management of the pancreatic remnant after pancreaticoduodenectomy involve a pancreatic–enteric anastomosis, usually either PJ or PG. Many variations of PJ have been reported, including the site of jejunum used (end *vs.* side), the type of anastomosis (invagination *vs.* duct-to-mucosa), the use of isolated Roux-en-Y limbs, and the use of pancreatic ductal stenting or fibrin glue.[17–22] A lack of agreement exists regarding the safest technique of PJ. Although limited experiments in dogs have favored a duct-to-mucosa technique over invagination[37] and stenting over no stenting,[19] prospective randomized human studies are lacking.

Pancreaticogastrostomy has gained favor in recent years as a potential means of reducing the incidence of pancreatic fistula after pancreaticoduodenectomy.[26–29] Proponents of PG have noted several potential advantages. First, the PG anastomosis can be easier to perform, because the posterior wall of the stomach lies immediately anterior to the mobilized pancreatic remnant and is always wider than the transected pancreatic neck. Second, with PG, the pancreatic exocrine secretions enter the potentially acidic gastric environment, where the low pH prevents their activation. In contrast with PJ, the activation of pancreatic exocrine secretions in PG can theoretically occur more easily in the presence of intestinal enterokinase and a neutral pH. Third, the performance of PG reduces the number of anastomoses in a single loop of retained jejunum, thereby potentially decreasing the likelihood of loop kinking. Published single-institution studies have favored PG over PJ,[38,39] although these studies are limited by their small patient populations, lack of randomization, and failure to document comparability between the two treatment groups with regard to risk factors for pancreatic fistula. Further, although a large meta-analysis has shown a significantly lower incidence of pancreatic fistula after PG as compared to end-to-end or end-to-side PJ, no significant differences in mortality were observed between the groups, and the definition of pancreatic fistula was not uniform among the studies included in the meta-analysis.[40]

The prospective, randomized, single-institution study presented in the current study was designed to test the hypothesis that PG is safer than PJ. The randomization provided comparable populations in the PG and PJ arms (Tables 1 and 2), and the primary study end point, the rate of pancreatic fistula, was similar in a comparison of PG and PJ (Table 3). Secondary study end points, such as the incidence of postoperative complications and the postoperative length of stay, were also similar between the PG and PJ groups (Table 3), thereby indicating no outcome advantage for either group. It is important to note that this study was performed in an institution with a high volume of pancreaticoduodenectomies per year[1,41] and by a group of surgeons with extensive experience in pancreatic resection. Although our data indicate no advantage of either PG or PJ regarding short-term outcomes, such as pancreatic fistula or other complications, additional follow-up is needed to evaluate differences in such parameters as patient survival or long-term pancreatic function.

The introduction of a newer technique (such as PG) into surgical practice is anticipated to result in a higher rate of early failure or complications, a phenomenon known as the "learning curve." In our institution, PJ was the standard means of restoring pancreatic–enteric continuity until 1991, at which time we began to use PG in selected cases. During the period of the current prospective randomized trial, no significant differences were observed in the rates of pancreatic fistula in a comparison of the first half of the trial to the second half, implying no role for a learning-curve phenomenon.

In earlier studies, researchers have evaluated the non-technical factors that predispose to pancreatic fistula after pancreatic–enteric anastomosis. The results were conflicting, but such factors as age older than 65 years, preoperative jaundice, small pancreatic duct, "soft" pancreas, emergency operation, and large intraoperative blood loss have all been associated with an increased risk of pancreatic fistula.[2,42,43] In the current study (Table 4), demographic factors, such as age, sex, and race, were not statistically associated with pancreatic fistula, nor were any preoperative history findings or laboratory values. Intraoperative parameters, such as increased operative time, increased blood replacement, and soft pancreatic texture, were found to positively correlate with the risk of pancreatic fistula on univariate analysis ($p < 0.05$).

However, these parameters failed to maintain their statistical significance in the multivariate model. No significant correlation was noted between the incidence of pancreatic fistula and other intraoperative or technical factors, such as length of mobilized pancreatic remnant, pancreatic duct diameter, inclusion of the pancreatic duct in the inner layer of the anastomosis, or drain contact with the anastomosis.

In the stepwise multivariate logistic regression analysis (Table 5), the two strongest predictors of pancreatic fistula were lower patient volume per surgeon and primary ampullary or duodenal disease. The correlation between patient volume per surgeon and pancreatic fistula was significant ($r = -0.91$; $p = 0.03$) and was associated with a generally increasing odds ratio for pancreatic fistula as the number of cases decreased. The association between pancreatic fistula and ampullary or duodenal disease was also strong, with odds ratios for pancreatic fistula of 5.43 and 12.63, respectively. Covariate analysis revealed that disease was significantly correlated with pancreatic texture ($p < 0.001$), but multivariate analysis revealed disease to be a better predictor of pancreatic fistula than texture.

In addition to the choice of PG *versus* PJ, another strategy proposed as a means of reducing the incidence of pancreatic fistula after pancreaticoduodenectomy involves the use of prophylactic octreotide therapy. Somatostatin and its octapeptide analogue, octreotide, have been reported to decrease the volume, amylase content, and bicarbonate content of pancreatic juice in human external pancreatic fistulas seen after pancreatic resection[44] or transplantation.[45] Such inhibition of pancreatic exocrine function serves as a rationale for the use of octreotide as prophylaxis against the development of pancreatic fistula for patients undergoing pancreaticoduodenectomy. Two recent multicenter prospective, randomized clinical trials involved evaluation of prophylactic octreotide administered to patients undergoing pancreatic surgery.[46,47] Both studies have reported a significant decrease in the rate of pancreatic fistula in their entire study populations, but neither demonstrated a significant reduction in the rate of pancreatic fistula in the subgroup of patients treated by pancreaticoduodenectomy.

In the current series, treatment for the 17 patients with pancreatic fistula included maintenance of intraoperatively placed drains for 14 patients (82%) and percutaneous drainage for 3 patients (18%). No patient required reoperation for drainage. All pancreatic fistulas closed without the need for completion pancreatectomy or revision of the pancreatic anastomosis. Adjuncts used in the treatment of pancreatic fistulas included octreotide (100%) and total parenteral nutrition (94%). For many patients with pancreatic fistula, oral intake was prohibited. For some patients with pancreatic fistula, radiographic studies performed through the intraoperatively placed drains revealed the drain to be in direct contact with the leaking pancreatic–enteric anastomosis. In these cases, the drain was advanced out a short distance, allowing the disrupted or leaking anastomosis to heal.

In the current study, pancreatic fistula significantly lengthened hospital stay and was often accompanied by other serious complications, such as delayed gastric emptying, cholangitis, and abscess formation (Table 6). Although there were no deaths among the patients studied, pancreatic fistula undoubtedly is associated with life-threatening complications, such as bleeding and sepsis. Additional studies, therefore, will be necessary to determine the safest means of performing a pancreatic–enteric anastomosis.

In conclusion, this prospective, randomized single-institution study has demonstrated that pancreatic fistula is a common complication after pancreaticoduodenectomy. Pancreatic fistula is most strongly associated with lower patient volume per surgeon and ampullary or duodenal disease. These data do not support the hypothesis that PG is safer than PJ or that it is associated with a lower incidence of pancreatic fistula.

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Discussion

DR. JONATHAN E. RHOADS (Philadelphia, Pennsylvania): This is a superb study and could hardly have been done anywhere else that I know of because they accumulated 145 cases in about 20 months in one institution. A little over half of the cases were done by one surgeon—and perhaps you can guess who that was. And I always wonder when considering the allocations of the risks to the experience of the surgeons, whether it is the experience that counts or whether it is the success of the surgeon that attracts the cases.

In any case, as you have heard, this operation was done first, I believe, by Dr. John Waugh, who unfortunately died rather early and did not extend the series. We became aware of the operation through a publication by Millbourn in the *Acta Chirurgia Scandinavica,* who reported seven successful cases in 1958. And he said that the procedure had been carried out in England between the time of John Waugh and Clagett's paper and his.

The reason we were interested in it is that we had had a bad experience with anastomosis to the jejunum. Our most fatal complication of pancreatic resection in the 1950s was hemorrhage. The pancreatic juice is activated by the succus entericus,